Depot-medroxyprogesterone versus norethisterone enantate for long-acting progestogenic contraception

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DMPA and NET-EN are similar in terms of their efficacy and safety, except that more women using DMPA experience amenorrhoea. Local knowledge about cultural attitudes to amenorrhoea may be used to choose between the two injectables.

RHL Commentary by Gray A

1. EVIDENCE SUMMARY

A systematic review has examined the differences between two progestogen-only injectable contraceptives, depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN) (1). Only evidence from randomized controlled trials (RCTs) in which DMPA was given at a dose of 150mg every 3 months and NET-EN at a dose of 200mg every 2 months were included.

Only two trials met the inclusion criteria. Both had been conducted under the auspices of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. One involved a single site and the other was a multi-site study. The multi-site study was reported separately for the 13 sites, and each of these was treated in the meta-analysis as a separate study. This study had recruited 10331 women, but data from a third arm (in which NET-EN was given every 2 months for 6 doses and every 3 months thereafter) were excluded. The single site study provided data from 400 women over 12 months. In total, data were available from 3572 women over 6 months, 2776 over 12 months and 2376 over 24 months of treatment.

No difference could be detected between the two treatments in the frequency of discontinuation at 12 months (the risk difference (RD) was 0.00, 95% confidence interval (CI) was between -0.06 and 0.06). There were no differences in the frequency of discontinuation due to accidental pregnancy, amenorrhoea, bleeding problems or other medical reasons. Users of NET-EN were, however, more likely to discontinue for personal reasons (RD -0.04; 95% CI -0.07 to -0.01). While the differences in bleeding or spotting (whether events or duration) at 12 and 24 months were not significant, there was a 21% higher risk of amenorrhoea in DMPA users at both time points (95% CI 8-35% at 12 months; 14-29% at 24 months). Weight changes and blood pressure changes were not significantly different. Importantly, no data were available on the major adverse effects of interest (vaginal shedding of HIV; susceptibility to HIV and other STIs). Data on bone mineral density would also not have been available from studies conducted in the 1970s and 1980s.

An extensive search was conducted, using the methods developed by the Cochrane Fertility Regulation Group. The authors did concede that, due to the time that had elapsed between completion of retrieved
studies and the review, few additional details could be obtained from the authors.

Data extraction for the review was done in the standard fashion, but the analysis was somewhat unusual in that the results from the 13 sites used in the 1977-1982 multi-site study were treated separately. The graphics therefore represent the results as if they were independent trials. Though not explained in any way, it was noted that loss to follow up varied considerably between the two included studies. The multi-site study reported a surprisingly low 1% loss over 2 years. In the shorter (1-year) single site study, 27% of DMPA users and 40% of NET-EN users were lost to follow up.

2. RELEVANCE TO UNDER-RESOURCED SETTINGS

2.1. Magnitude of the problem

The patterns of hormonal contraceptive use vary considerably between settings, and reflect local preferences as well as provider biases (1, 2). In resource-constrained settings, programme managers may be under pressure to reduce the range of method options. Where such choices can be made without unnecessarily restricting access to meaningfully different methods, identifying methods that are substantially the same may provide opportunities for rational choices. Both DMPA and NET-EN are extensively used in developing countries, but may be priced very differently. This can have a considerable impact on health expenditure. South Africa provides one such example (3). In other countries the acquisition costs may be closer, but total programmatic costs may still be higher where the dose frequency is higher. Based on data from the Management Sciences for Health International Drug price Indicator Guide 2005, the acquisition cost per couple-year of protection in Namibia was $6.0056 for DMPA and $6.2094 for NET-EN (4). Both DMPA and NET-EN appear on the core list of the WHO Model Essential Medicines List (14th edition)(5). A recent cross-sectional study in 893 South African women has shown that expressed preferences for DMPA or NET-EN were based on misperceptions (6). Women who preferred DMPA thought it was more effective in preventing pregnancy, whereas those who preferred NET-EN believed that return to fertility was more likely with this agent.

2.2. Applicability of the results

The data included in this systematic review were generated in a variety of settings. The single site study was conducted in Egypt, and the multi-site study in developed (Luxembourg, Italy, the Netherlands), transitional (Yugoslavia) and developing (Egypt, Thailand, Nigeria, Pakistan, Zambia, Philippines, Mexico, Brazil, Chile) countries. Attitudes towards the one significant difference detected between DMPA and NET-EN (amenorrhoea) may well be important in determining discontinuation rates in a particular setting.

2.3. Implementation of the intervention

Structures entrusted with medicines selection need to carefully consider whether to provide both of these progestogen-only injectable contraceptives. Efforts to widen contraceptive choices may entail making choices between these and once-a-month injectables or longer-acting implantable contraceptives. Local knowledge about cultural attitudes to amenorrhoea may help guide such decisions. However, other endpoints may be considered to be more important, and the evidence for such endpoints may not as yet be available. Some data on endpoints not considered in the review are available, such as on the effect of progestogen-only injectable contraceptives on carbohydrate metabolism (7) and lipids (8). Newer presentations of progestogen-only contraceptives have become available. Subcutaneous administration of DMPA has, however, been shown to be associated with amenorrhoea, with an increase over time of use (9). Bleeding patterns in users of once-a-month combined injectable contraceptives are also not normal (10). Choosing between alternative injectable methods on this criterion alone is therefore difficult.
3. RESEARCH

Future research needs to focus on two areas of concern – the effect of the long-acting injectable contraceptives on bone health and HIV risk.

Systematic reviews of the available evidence for the effects of combined hormonal contraceptives (11) and progestogen-only contraceptives (12) on bone health have recently been published. The second of these concluded that “[limited evidence suggested that the use of progestogen-only contraceptives other than DMPA did not affect [bone mineral density]”. Although recovery of bone mineral density (BMD) after discontinuation of DMPA has been shown (13), sequential use of DMPA and then a combined oral contraceptive may also be problematic (14). More recently still, it has been reported that once-a-month combined injectable contraceptives did not have a measurable effect on BMD (15). Until more evidence of a significant difference between injectable contraceptives is available, it would seem prudent to follow the advice given by the WHO (16). Noting that “there should be no restriction on the use of DMPA, including no restriction on duration of use, among women aged 18–45 years who are otherwise eligible to use the method”, the WHO also stated that “recommendations regarding DMPA use also pertain to the use of NET-EN”. This is in line with the advice provided by the Society for Adolescent Medicine in the United States, which has recommended “to continue prescription of DMPA, with counseling about the risks and benefits, in most of the adolescent population desiring to use this contraceptive method” (17).

Further data are also needed before any new recommendations can be made regarding the use of hormonal contraceptives (including injectables) and increased risk of acquiring HIV or other STIs. A 2005 statement released after a WHO regional meeting in Nairobi stated that “[t]here should be no restrictions on the use of COCs and DMPA by women at risk of acquiring HIV, consistent with the current WHO Medical Eligibility Criteria for Contraceptive Use guidelines” (18).

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References


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